PATENT
1718-0195P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	QUIBELL, Martin et al.	Conf.:	8544
Appl. No.:	10/015,186	Group:	1614
Filed:	November 16, 2001	Examiner:	UNASSIGNED
For:	CYSTEIN PROTEASE INHIBITORS		

L E T T E R

Assistant Commissioner for Patents
Washington, DC 20231

August 5, 2002

Sir:

Under the provisions of 35 U.S.C. § 119 and 37 C.F.R. § 1.55(a), the applicant(s) hereby claim(s) the right of priority based on the following application(s):

Country	Application No.	Filed
UNITED KINGDOM	9911417.5	May 18, 1999
PCT/GB	00/01894	May 18, 2000

A certified copy of the above-noted application(s) is(are) attached hereto.

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BIRCH, STEWART, KOLASCH & BIRCH, LLP

(Signature)

August 5, 2002 (Date of Signature)

LRS/SWG/sbp
1718-0195P

Respectfully submitted,

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Attachment

(Rev. 10/31/01)

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Concept House
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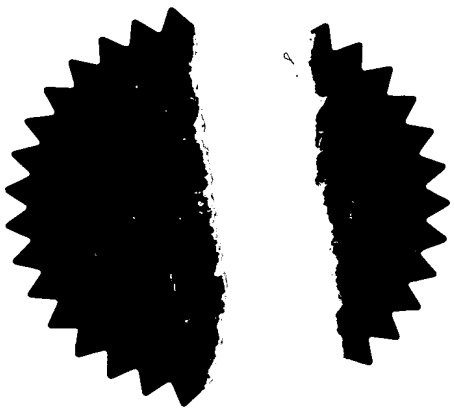

Signed R. Mahoney

Dated -6 DEC 2001

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Request for grant of a patent

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Cardiff Road
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1.	Your reference	40655/JMD
2.	Patent application number *(The Patent Office will fill in this part)*	**9911417.5**
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	PEPTIDE THERAPEUTICS LIMITED Peterhouse Technology Park, 100, Fulbourn Road, Cambridge CB1 9PT.
	Patents ADP number *(if you know it)*	6427[illegible]8007003
	If the applicant is a corporate body, give the country/state of incorporation	United Kingdom
4.	Title of the invention	Furanone Derivatives as Inhibitors of Cathepsin S
5.	Full name, address and postcode in the United Kingdom to which all correspondence relating to this form and translation should be sent	Reddie & Grose 16 Theobalds Road LONDON WC1X 8PL
	Patents ADP number *(if you know it)*	91001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application *(If you know it)*	Date of filing *(day/month/year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day/month/year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*
   a) any applicant named in part 3 is not an inventor, or
   b) there is an inventor who is not named as an applicant, or
   c) any named applicant is a corporate body.
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Continuation sheets of this form	
Description	25
Claim(s)	7
Abstract	0
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Priority documents	0
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	0
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	0
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature: Reddie & Grose

Date: 17 May 1999

12. Name and daytime telephone number of person to contact in the United Kingdom

J M DAVIES
01223-360350

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Notes

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Furanone Derivatives as Inhibitors of Cathepsin S

Field of the invention.

Cathepsin S is a highly active cysteine protease belonging to the papain superfamily. Its primary structure is 57%, 41% and 45% homologous with that of the human cathepsin L and H and plant cysteine proteases papain respectively, although only 31% homologous with Cathepsin B.

It is found mainly in lymph nodes, spleen, and macrophages and this limited occurrence suggests the potential involvement of this enzyme in the pathogenesis of degenerative disease.

Moreover, it has been found that destruction of Ii by proteolysis is required for MHC class II molecules to bind antigenic peptides, and for transport of the resulting complex to the cell surface. Furthermore, it has been found that Cathepsin S is essential in B cells for effective Ii proteolysis necessary to render class II molecules competent for binding peptides. Therefore, the inhibition of this enzyme may be useful in modulating class II-restricting immune response (WO 97/40066).

Selective inhibition of a single protease in a complex mixture of proteolytic enzymes and more especially over other members of the same enzyme class or family is imperative as incorrect regulation of proteolytic activity can lead to unwanted pathological conditions such as hypertension, blood clotting or

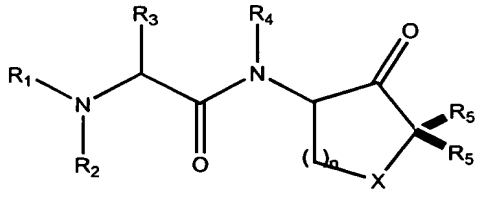
worse. This has lead to the search for inhibitors that selectively inhibit only one member of a proteolytic family, a problem that is very relevant to the Cathepsin family, which have a high degree of homology.

The invention relates to novel protease inhibitors, particularly inhibitors of the cysteine proteases of the papain superfamily and more particularly to Cathepsin S. The inhibitors of the invention are selective over other members of the family and in particular show selectively over other members of the Cathepsin family such as L and K.

Description of the related art.

In WO 97/40066, the use of inhibitors against Cathepsin S is described. The inhibition of this enzyme is suggested to prevent or treat disease caused by protease activity.

WO 98/50533 describes the use of compounds according to the formula (I).



(I)

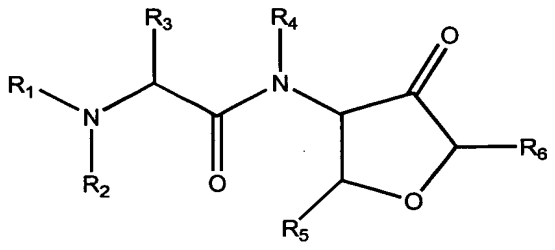
It is suggested the compounds of this formula, known as the tetrahydrofuran-3-ones, are useful as inhibitors to proteases,

in particular the papain superfamily; specifically those of the Cathepsin family; and particularly Cathepsin K.

Summary of the invention

The present invention provides compounds which inhibit the cysteine protease Cathepsin S but do not significantly inhibit other members of the papain superfamily. The compounds of the present invention are useful for the treatment of diseases caused by or enhanced by the presence or the activity of the protease enzyme.

Accordingly, the first aspect of the invention provides a compound according to formula (II):

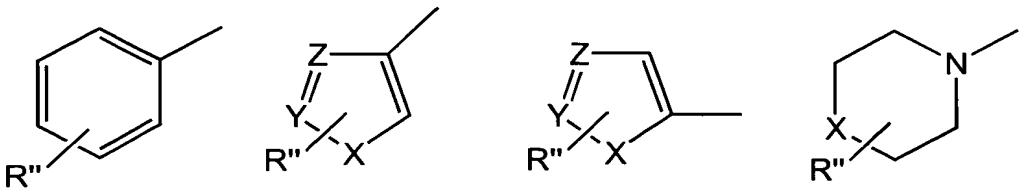


(II)

wherein:

R1 = R' , R'C(O) , R' C(S), R' SO2 , R' OC(O), R' NHC(O)

R′ =



X, = O, S, NH, Y, Z = CH, N:

R′′ = single or multiple ring substitution combinations taken from:

H, C1-7-alkyl, C3-6-cycloalkyl, OH, SH, NH2, Halogen;

R2, R4 = H, C1-7-alkyl, C3-7-cycloalkyl,

R3 = C1-7-alkyl, C3-7-cycloalkyl;

R5 = C1-7-alkyl, Halogen, Ar- C1-7-alkyl, C1-3-alkyl-CONR′′′, R^{iv}; and

R6 = C1-7-alkyl, Ar- C1-7-alkyl; C1-3-alkyl-SO2-R^{v}, C1-3-alkyl-C(O)-NHR^{v}.

'C1-7-alkyl' as applied herein is meant to include straight and branched chain aliphatic carbon chains such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl, heptyl and any simple isomers thereof. Additionally, any C1-7-alkyl may optionally be substituted by one or two halogens F, Cl, Br and or a heteroatom S, O, NH. If the heteroatom is located at a chain terminus then it is appropriately substituted with one or 2 hydrogen atoms.

'Halogen' as applied herein is meant to include F, Cl, Br, I.

'C3-6-cycloalkyl' as applied herein is meant to include any variation of 'C1-7-alkyl' which additionally contains a carbocyclic ring such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

'Ar- C1-7-alkyl' as applied herein is meant to include any unsubstituted phenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazinolyl, isothiazinolyl, thiazolyl, oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, furanyl, thienyl aromatic ring (Ar) attached through a 'C1-7-alkyl' (defined above) to the dihydro-(3H)-furanone ring system. Optionally, the aromatic ring may be substituted with halogen, C1-3-alkyl, OH, OC1-3-alkyl, SH, SC1-3-alkyl, NH_2, NHC1-3-alkyl, N(C1-3-alkyl) 2, where C1-3-alkyl includes methyl, ethyl, propyl, isopropyl, cyclopropyl.

'C1-3-alkyl-CONR''', R^{iv}' as applied herein is meant to include straight or branched carbon chain substituted with a 1°, 2° or 3° carboxamide wherein R''', R^{iv} includes H and Me.

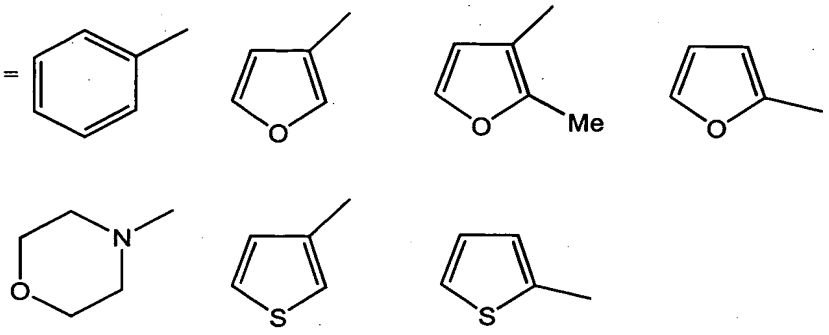
'C1-3-alkyl-SO_2-R^v' as applied herein is meant to include straight or branched carbon chain substituted with a sulphone wherein R^v includes 'C1-7-alkyl', 'Ar- C1-7-alkyl', 'C3-6-cycloalkyl'.

'C1-3-alkyl-C(O)-NHR^{v}' as applied herein is meant to include straight or branched carbon chain substituted with a secondary carboxamide wherein R^{v} includes 'C1-7-alkyl', 'Ar- C1-7-alkyl', 'C3-6-cycloalkyl'.

If a chiral centre is present, all isomeric forms are intended to be covered.

Suitably compounds of the present invention have

R1 = R'C(O)

Where R' = 

R2 and R4 = H;

R3 = n-butyl, 3-(2,2-dimethylpropyl), 4-(2-methylbutyl), 4-(3,3-dimethylbutyl);

R5 = CH_3, C_2H_5, CH_2Ar, CH_2CONH_2, Both (R) and (S) stereochemistries with (S) being preferred;

R6 = H, CH_2-X-Ar, X = O, S, NH.

Compounds of the present invention include but are not limited to the following examples;

Dihydro-(4-(S)-Amino-N-[(3-furanoyl)-L-tButyl-L-alanine])-5-(R)-methyl)-3(2H)-furanone;

Dihydro-(4-(R)-Amino-N-[(3-furanoyl)-L-tButyl-L-alanine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(3-furanoyl)-L-tButyl-L-alanine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(3-thienoyl)-L-tButyl-L-alanine])-5-(R)-methyl)-3(2H)-furanone;

Dihydro-(4-(R)-Amino-N-[(3- thienoyl)-L-tButyl-L-alanine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(3- thienoyl)-L-tButyl-L-alanine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(3-furanoyl)-L-homoleucine])-5-(R)-methyl)-3(2H)-furanone;

Dihydro-(4-(R)-Amino-N-[(3-furanoyl)-L- homoleucine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(3-furanoyl)-L- homoleucine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(3-thienoyl)-L- homoleucine])-5-(R)-methyl)-3(2H)-furanone;

Dihydro-(4-(R)-Amino-N-[(3- thienoyl)-L- homoleucine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(3- thienoyl)-L- homoleucine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(morpholinocarbamoyl)-L-tButyl-L-alanine])-5-(R)-methyl)-3(2H)-furanone;

Dihydro-(4-(R)-Amino-N-[(morpholinocarbamoyl)-L-tButyl-L-alanine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(morpholinocarbamoyl)-L-tButyl-L-alanine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(morpholinocarbamoyl)-L-homoleucine])-5-(R)-methyl)-3(2H)-furanone;

Dihydro-(4-(R)-Amino-N-[(morpholinocarbamoyl)-L- homoleucine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(morpholinocarbamoyl)-L- homoleucine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(benzoyl)-L-tButyl-L-alanine])-5-(R)-methyl)-3(2H)-furanone;

Dihydro-(4-(R)-Amino-N-[(benzoyl)-L-tButyl-L-alanine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(benzoyl)-L-tButyl-L-alanine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(benzoyl)-L-homoleucine])-5-(R)-methyl)-3(2H)-furanone;

Dihydro-(4-(R)-Amino-N-[(benzoyl)-L- homoleucine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(benzoyl)-L- homoleucine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(3-(2-methyl)furanoyl)-L-tButyl-L-alanine])-5-(R)-methyl)-3(2H)-furanone;

Dihydro-(4-(R)-Amino-N-[(3-(2-methyl)furanoyl)-L-tButyl-L-alanine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(3-(2-methyl)furanoyl)-L-tButyl-L-alanine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(3-(2-methyl)furanoyl)-L-homoleucine])-5-(R)-methyl)-3(2H)-furanone;

Dihydro-(4-(R)-Amino-N-[(3-(2-methyl)furanoyl)-L-homoleucine])-5-(S)-methyl)-3(2H)-furanone;

and

Dihydro-(4-(S)-Amino-N-[(3-(2-methyl)furanoyl)-L-homoleucine])-5-(S)-methyl)-3(2H)-furanone.

Experimental

1) Preparation of Building Blocks

(a) General method for the synthesis of diazoketones, exemplified by (2*S*,3*R*)-*N*-9-fluorenylmethoxycarbonyl-*O*-*t*-butyl-L-threonyldiazomethane (1).

(2*S*,3*R*)-*N*-9-Fluorenylmethoxycarbonyl-*O*-*t*-butyl-L-threonine (1.99 g, 5 mmol) was dissolved in dry THF (20 mL) and *N*-methylmorpholine (1.21 mL, 11 mmol) added. The reaction mixture was cooled to -15°C and stirred under an atmosphere of argon. Isobutyl chloroformate (0.72 mL, 5.5 mmol) was added and the

mixture stirred for 10 min at -15°C before a solution of diazomethane in diethyl ether (100 mL, approx. 20 mmol) was added. The reaction was allowed to warm to room temperature over one hour. Acetic acid was added dropwise until effervescence had ceased and the reaction mixture was then diluted with ethyl acetate (150 mL), washed with saturated aqueous sodium bicarbonate (2 x 75 mL), water (75 mL) and brine (75 mL) and dried over sodium sulphate. The solvent was removed *in vacuo* to give crude (2*S*,3*R*)-*N*-9-fluorenylmethoxycarbonyl-*O*-*t*-butyl-L-threonyldiazomethane (2.11g, 100%) as a pale yellow immobile oil. This compound was carried through to the next stage without further purification. Electrospray-MS m/z 444 (MNa^+, 20%), 394 ($MH^+ - N_2$, 70%) and 338 (MH^+ -*t*butyl - N_2, 100%).

(2*R*,3*S*)-*N*-9-Fluorenylmethoxycarbonyl-*O*-*t*-butyl-D-threonyldiazomethane (2)

This compound was synthesised from (2*R*,3*S*)-*N*-9-fluorenylmethoxycarbonyl-*O*-*t*-butyl-D-threonine using the above method on a 1 mmol scale to give 480 mg (111 %) of a pale yellow oil. Electrospray-MS m/z 394 ($MH^+ - N_2$, 60%) and 338 (MH^+ - *t*butyl - N_2, 100%).

(2*S*,3*S*)-*N*-9-Fluorenylmethoxycarbonyl-*O*-*t*-butyl-L-*allo*-threonyldiazomethane(3)

This compound was synthesised from (2*S*,3*S*)-*N*-9-fluorenylmethoxycarbonyl-*O*-*t*-butyl-L-*allo*-threonine using the above method on a 1 mmol scale to give 531 mg (123 %) of a pale yellow oil. Electrospray-MS m/z 394 ($MH^+ - N_2$, 90%) and 338 (MH^+ - *t*butyl - N_2, 60%).

(2*S*)-*N*-9-Fluorenylmethoxycarbonyl-*O*-*t*-butyl-L-serinyldiazomethane (4)

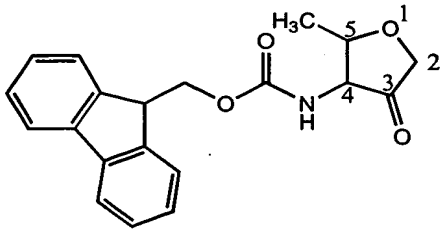
This compound was synthesised from (2*S*)-*N*-9-fluorenylmethoxycarbonyl-*O*-*t*-butyl-L-serine using the above method on a 3 mmol scale to give 1.67 g (136 %) of a pale yellow oil. Electrospray-MS m/z 430 (MNa^+, 5%), 380 ($MH^+ - N_2$, 12%) and 324 (MH^+ - *t*butyl - N_2, 28%).

(2*R*)-*N*-9-Fluorenylmethoxycarbonyl-*O*-*t*-butyl-D-serinyldiazomethane (5)

was synthesised from (2*R*)-*N*-9-fluorenylmethoxycarbonyl-*O*-*t*-butyl-D-serine using the above method on a 1 mmol scale to give 476 mg (116 %) of a pale yellow oil. Electrospray-MS m/z 380 ($MH^+ - N_2$, 55%) and 324 (MH^+ - *t*butyl - N_2, 52%).

(b) Synthesis of Dihydro-3(2H)-Furanones

General method for the synthesis of dihydro-4-(*N*-9-fluorenylmethoxycarbonyl amino)-5-methyl-3(2H)-furanones



A solution of lithium chloride (50 mmol) in 80% aqueous acetic acid (80 mL) was cooled to 5°C and added to *N*-9-fluorenylmethoxycarbonyl-*O*-*t*-butylthreonyldiazomethane (**1-3**, 5

mmol). The mixture was stirred until the substrate dissolved and then for one additional hour. The solvents were removed *in vacuo* and the residue partitioned between EtOAc (3 x 100 mL) and 10% aqueous Na_2CO_3 (100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. Purification by flash silica chromatography eluting with EtOAc:heptane (35:65) yielded the following compounds as white solids:

(4*S*,5*R*)-Dihydro-4-(*N*-9-fluorenylmethoxycarbonylamino)-5-methyl-3(2H)-furanone (6)

69% yield; Electrospray-MS m/z 338 (MH^+, 100%); HPLC rt 14.59 min; ^1H NMR ($CDCl_3$, 500 MHz) 7.76 (2H, d, J = 7.4 Hz, Ar-H), 7.58 (2H, d, J = 7.4 Hz, Ar-H), 7.41 (2H, t, J = 7.4 Hz, Ar-H), 7.32 (2H, t, J = 7.4 Hz, Ar-H), 5.11 (1H, brs, NH), 4.44 (2H, brd, Fmoc-CH_2), 4.25 (1H, d, J = 17.7 Hz, H-2), 4.22 (1H, t, J = 6.7 Hz, Fmoc-9), 3.99 (1H, d, J = 17.7 Hz, H-2), 3.97 (1H, brm, H-5), 3.80 (1H, brt, H-4), 1.50 (3H, brd, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) 211.8 (C-3), 156.1 (FmocC=O), 143.7 (Ar-4°), 141.4 (Ar-4°), 127.8 (Ar-H), 127.1 (Ar-H), 125.0 (Ar-H), 120.1 (Ar-H), 77.4 (C-5), 70.8 (C-2), 67.3 (FmocCH_2), 62.7 (C-4), 47.2 (Fmoc-9), 19.1 (CH_3).

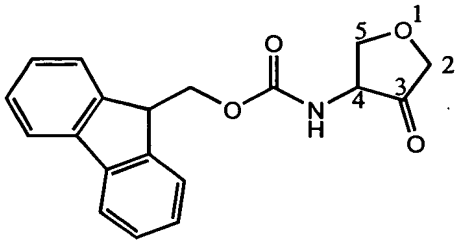
(4*R*,5*S*)-Dihydro-4-(*N*-9-fluorenylmethoxycarbonylamino)-5-methyl-3(2H)-furanone (7)

70% yield; Electrospray-MS m/z 338 (MH^+, 75%); HPLC rt 14.62 min.

(4*S*,5*S*)-Dihydro-4-(*N*-9-fluorenylmethoxycarbonylamino)-5-methyl-3(2H)-furanone (8)

64% yield; Electrospray-MS m/z 338 (MH^+, 100%); HPLC rt 14.68 min.

General method for the synthesis of dihydro-4-(*N*-9-fluorenylmethoxycarbonyl amino)-3(2H)-furanone



A solution of lithium chloride (30 mmol) in 80% aqueous acetic acid (80 mL) was cooled to 5°C and added to *N*-9-fluorenylmethoxycarbonyl-*O*-*t*-butylserinyldiazomethane (**4-5**, 3 mmol). The mixture was stirred until the substrate dissolved and then for one additional hour. The solvents were removed *in vacuo* and the residue partitioned between EtOAc (3 x 80 mL) and 10% aqueous Na_2CO_3 (80 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and the solvents removed *in vacuo*. Purification by flash silica chromatography eluting with EtOAc:DCM (2.5:97.5) to remove impurities and then EtOAc:DCM (4:96) yielded the following compounds as white solids:

(4*S*)-Dihydro-4-(*N*-9-fluorenylmethoxycarbonylamino)-3(2H)-furanone (9)

74% yield; Electrospray-MS m/z 324 (MH^+, 75%); HPLC rt 13.97 min; ^1H NMR ($CDCl_3$, 500 MHz) 7.77 (2H, d, J = 7.4 Hz, Ar-H), 7.58 (2H,

d, J = 7.4 Hz, Ar-H), 7.41 (2H, t, J = 7.4 Hz, Ar-H), 7.32 (2H, t, J = 7.4 Hz, Ar-H), 5.20 (1H, s, NH), 4.69 (1H, t, J = 8.4 Hz, H-5), 4.43 (2H, d, J = 6.3 Hz, Fmoc-CH_2), 4.21 (3H, m, Fmoc-9, H-4, H-2), 3.94 (1H, d, J = 17.5 Hz, H-2), 3.78 (1H, t, J = 9.5 Hz, H-5); ^{13}C NMR ($CDCl_3$, 100 MHz) 211.2 (C-3), 156.0 (FmocC=O), 143.6 (Ar-4°), 141.4 (Ar-4°), 127.8 (Ar-H), 127.1 (Ar-H), 125.0 (Ar-H), 120.1 (Ar-H), 70.7 (C-5), 70.0 (C-2), 67.4 (FmocCH_2), 56.1 (THF-4), 47.1 (Fmoc-9).

(4*R*)-Dihydro-4-(*N*-9-fluorenylmethoxycarbonylamino)-3(2H)-furanone (10)

78% yield; Electrospray-MS m/z 324 (MH^+, 100%); HPLC rt 14.05 min.

(c) Preparation of Building Block-Linker Constructs

General method for the synthesis of Dihydro-3(2H)-Furanone - Linker Constructs (11-15)

Dihydro-3(2H)-furanone **6-10**, (1.0eq) was dissolved in a mixture of ethanol / water (7:1 v/v, 10mL per mmole compound) containing sodium acetate trihydrate (1.5eq). 4-[[(hydrazinocarbonyl)amino]methyl]cyclohexanecarboxylic acid. trifluoroacetate (mw 329.3, 1.0eq) was added and the mixture heated under reflux for 2hrs. The mixture was then cooled, poured into dichloromethane (100mL per mmole compound) and water (100mL) added. The organic layer was separated, backwashed with saturated brine (100mL). The organic layer was

dried (Na_2SO_4), filtered and evaporated *in vacuo* to yield a white solid. Yield 85 - 105% crude weight.
Constructs **11-15** were used without further purification

(d) Loading of Macrocrowns With Constructs

General method for the Loading of Multipins with Dihydro-3(2H)-Furanone - Linker Constructs (11-15)

Amino functionalised DA/MDA macrocrowns (ex Chiron Mimotopes, Australia, 9.1µmole loading) or amino functionalised HEMA gears (ex Chiron Mimotopes, Australia, 1.3µmole loading) were used for all loadings and subsequent solid phase syntheses.

Dihydro-3(2H)-Furanone - Linker Construct (**11-15**) (3eq compared to total surface functionalisation of crowns / gears) was carboxyl activated with 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (3eq), 1-hydroxybenzotriazole (3eq) and N-methylmorpholine (6eq) in dimethylformamide (5mL) for 5mins. This mixture was added to the crowns / gears, additional DMF added to cover the reaction surface and the mixture left overnight.

Standard washing and Fmoc deprotection readings (see procedures below) indicated virtually quantitative loading.

2) General Solid Phase procedures

All final molecules were assembled using solid phase procedures on Chiron multipins following the protocols detailed below.

Preparation of Crown Assembly

The compounds were synthesised in parallel fashion using the appropriately loaded Fmoc-Building block-linker-DA/MDA derivatised macrocrowns (see above) loaded at approximately 3.5 - 9.1 μmoles per crown. Prior to synthesis each crown was connected to its respective stem and slotted into the 8 x 12 stem holder. Coupling of the amino acids employed standard Fmoc amino acid chemistry as described in `Solid Phase Peptide Synthesis', E. Atherton and R.C. Sheppard, IRL Press Ltd, Oxford, UK, 1989.

Removal of Nα-Fmoc Protection

A 250 mL solvent resistant bath is charged with 200 mL of a 20% piperidine/DMF solution. The multipin assembly is added and deprotection allowed to proceed for 30 minutes. The assembly is then removed and excess solvent removed by brief shaking. The assembly is then washed consecutively with (200 mL each), DMF (5 minutes) and MeOH (5 minutes, 2 minutes, 2 minutes) and left to air dry for 15 minutes.

Quantitative UV Measurement of Fmoc Chromophore Release

A 1 cm path length UV cell is charged with 1.2 mL of a 20% piperidine/DMF solution and used to zero the absorbance of the UV spectrometer at a wavelength of 290nm. A UV standard is then prepared consisting of 5.0 mg Fmoc-Asp(OBut)-Pepsyn KA (0.08 mmol/g) in 3.2 mL of a 20% piperidine/DMF solution. This

standard gives Abs_{290} = 0.55-0.65 (at room temperature). An aliquot of the multipin deprotection solution is then diluted as appropriate to give a theoretical Abs_{290} = 0.6, and this value compared with the actual experimentally measured absorbance showing the efficiency of previous coupling reaction.

Standard Coupling Of Amino Acid Residues

Coupling reactions are performed by charging the appropriate wells of a polypropylene 96 well plate with the pattern of activated solutions required during a particular round of coupling. Macrocrown standard couplings were performed in DMF (500 µl).

Coupling of an Amino-acid Residue To Appropriate Well

Whilst the multipin assembly is drying, the appropriate N_α-Fmoc amino acid pfp esters (10 equivalents calculated from the loading of each crown) and HOBt (10 equivalents) required for the particular round of coupling are accurately weighed into suitable containers. Alternatively, the appropriate N_α-Fmoc amino acids (10 equivalents calculated from the loading of each crown), desired coupling agent e.g. HBTU (9.9 equivalents calculated from the loading of each crown) and activation e.g. HOBt (9.9 equivalents calculated from the loading of each crown), NMM (19.9 equivalents calculated from the loading of each crown) are accurately weighed into suitable containers.

The protected and activated Fmoc amino acid derivatives are then dissolved in DMF (500 µl for each macrocrown e.g. for 20

macrocrowns, 20 x 10 eq. x 7 µmoles of derivative would be dissolved in 10 mL DMF). The appropriate derivatives are then dispensed to the appropriate wells ready for commencement of the 'coupling cycle'. As a standard, coupling reactions are allowed to proceed for 6 hours. The coupled assembly was then washed as detailed below.

Washing Following Coupling

If a 20% piperidine/DMF deprotection is to immediately follow the coupling cycle, then the multipin assembly is briefly shaken to remove excess solvent washed consecutively with (200 mL each), MeOH (5 minutes) and DMF (5 minutes) and de-protected. If the multipin assembly is to be stored or reacted further, then a full washing cycle consisting brief shaking then consecutive washes with (200 mL each), DMF (5 minutes) and MeOH (5 minutes, 2 minutes, 2 minutes) is performed.

Addition of Capping Group

Whilst the multipin assembly is drying, the appropriate acid capping group (10 equivalents calculated from the loading of each crown), desired coupling agent e.g. HBTU (9.9 equivalents calculated from the loading of each crown) and activation e.g. HOBt (9.9 equivalents calculated from the loading of each crown), NMM (19.9 equivalents calculated from the loading of each crown) are accurately weighed into suitable containers. The acid derivatives / coupling agents are then dissolved in DMF (500 µl for each macrocrown e.g. for 20 macrocrowns, 20 x 10 eq. of derivative would be dissolved in 10 mL DMF) and left to activate for 5 minutes. The appropriate derivatives are then

dispensed to the appropriate wells ready for commencement of the 'capping cycle'. As a standard, capping reactions are allowed to proceed for 18 hours overnight. The capped assembly was then washed as detailed above.

Acidolytic Mediated Cleavage of Molecule-Pin Assembly

Acid mediated cleavage protocols are strictly performed in a fume hood. A polystyrene 96 well plate (1 mL/well) is labelled, then the tare weight measured to the nearest mg. Appropriate wells are then charged with a trifluoroacetic acid/water (95:5, v/v, 600 µl) cleavage solution, in a pattern corresponding to that of the multipin assembly to be cleaved.

The multipin assembly is added, the entire construct covered in tin foil and left for 2 hours. The multipin assembly in then added to another polystyrene 96 well plate (1 mL/well) containing trifluoroacetic acid/water (95:5, v/v, 600 □l) (as above) for 5 minutes.

Work up of Cleaved Molecules

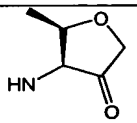
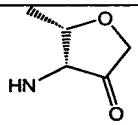
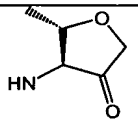
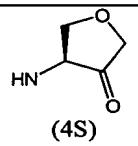
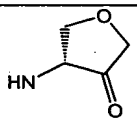
The primary polystyrene cleavage plate (2 hour cleavage) and the secondary polystyrene plate (5 minute wash) are then placed in the GeneVac evaporator and the solvents removed (minimum drying rate) for 90 minutes. The contents of the secondary polystyrene plate are transferred to their corresponding wells on the primary plate using an acetonitrile/water (50: 50 v/v/v) solution (3 x 150 µl) and the spent secondary plate discarded.

Each of the multiple wells containing a particular molecule are combined and purified by semi-preparative reverse phase HPLC, using Vydac C_4.

Final Lyophilisation and Analysis of Molecules

Appropriate fractions are combined and lyophilised in tared 10mL glass vials, then re-weighed. Molecules were prepared on a 15-90μmole scale, yielding 2.0-26.0mg of purified products. The purity of each product was confirmed by analytical HPLC at >95% (215nm UV detection) and gave the appropriate $[M + H]^+$ by electrospray mass spectrometry analysis.

Molecules prepared by the methods detailed above are shown in Table 1, together with a Ki (μM) measurement of inhibition verses cathepsins S, L and K.

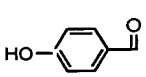
	P1				
CAP-P2	 (4S, 5R)	 (4R, 5S)	 (4S, 5S)	 (4S)	 (4R)
CAP1-L-Leu	0.49 0.48 0.083	0.23 2.7 0.41	0.17 2.04 0.32	0.23 0.24 0.07	0.27 0.39 0.07
CAP2-L-Leu					
CAP3-L-Leu	0.43 0.31 0.43			0.36 0.15 0.21	
CAP4-L-Leu					
CAP5-L-Leu	0.48 1.48 0.29				
CAP6-L-Leu	0.51 0.12 0.44	0.61 1.10 0.75	0.68 0.67 2.75	0.55 0.14 0.44	0.48 0.19 0.33
CAP7-L-Leu	2.8 0.69 0.015	4.2 6.8 0.17	3.7 4.9 0.15	3.1 0.69 0.018	3.9 1.1 0.023
CAP8-L-Leu		0.39 28.4			

		3.7			
CAP9-L-Leu		0.80 7.9 4.8			
CAP10-L-Leu	1.3 0.71 3.0				
CAP1-L-Nle		0.57 21.1 13.4	0.40 19.3 8.9	0.56 3.3 1.4	0.49 4.4 1.15
CAP2-L-Nle					
CAP3-L-Nle				0.76 2.8 5.8	
CAP4-L-Nle					
CAP5-L-Nle					
CAP6-L-Nle					
CAP7-L-Nle	4.1 10.5 0.24	6.8 46.7 3.1	6.2 49.9 1.3	5.4 10.2 0.26	5.7 15.2 0.13
CAP8-L-Nle	1.5 54.4 13.2	1.0 >100 >100			
CAP9-L-Nle					
CAP10-L-Nle					
CAP1-L-Tyr		1.0 1.8 >100	0.77 1.4 >100	0.86 0.33 27.1	0.72 0.35 >100
CAP2-L-Tyr	3.2 0.22 >100				
CAP3-L-Tyr	1.1 0.17 >100	0.17 1.4 >100	1.3 1.0 >100	1.6 0.25 >100	1.8 0.36 >100
CAP4-L-Tyr					
CAP5-L-Tyr	1.6 0.5 >100				
CAP6-L-Tyr	2.0 0.055 >100	0.24 0.67 >100	2.7 0.25 >100	1.5 0.14 >100	2.3 0.14 >100
CAP7-L-Tyr	7.4 0.24 2.8				
CAP8-L-Tyr		1.2 9.5 >100			
CAP9-L-Tyr					
CAP10-L-Tyr	4.8 0.06 >100	0.34 0.46 >100	4.1 0.45 >100	3.7 0.1 >100	3.7 0.1 >100
CAP1-L-hLeu	0.68 15.1 3.1	0.3 29.8 24.1			
CAP2-L-hLeu					
CAP3-L-hLeu				0.8 5.1 6.6	
CAP4-L-hLeu	3.2 55.8 13.0				
CAP5-L-hLeu					
CAP6-L-hLeu					

CAP7-L-hLeu					
CAP8-L-hLeu	0.97 38.9 16.0	0.45 >100 >100	0.37 >100 >100	0.66 49.7 16.3	0.44 61.2 8.7
CAP9-L-hLeu	0.78 48.7 34.3	0.7 >100 >100	0.52 >100 >100	0.25 71.5 21.6	0.46 58.2 16.4
CAP10-L-hLeu					
CAP1-L-tBu-Ala	0.25 3.9 0.39				
CAP2-L-tBu-Ala					
CAP3-L-tBu-Ala	0.42 6.6 0.85				
CAP4-L-tBu-Ala	0.94 87.1 5.7				
CAP5-L-tBu-Ala	0.47 24.6 0.65				
CAP6-L-tBu-Ala					
CAP7-L-tBu-Ala	2.7 13.1 0.04				
CAP8-L-tBu-Ala	0.18 39.0 1.3	0.2 >100 19.9	0.1 >100 7.3	0.21 36.4 0.85	0.24 68.1 0.91
CAP9-L-tBu-Ala	0.58 30.4 4.2				
CAP10-L-tBu-Ala					

Table 1. Ki competitive inhibition measurements (μM) vs Cathepsin S
L
K

CAP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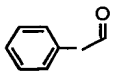
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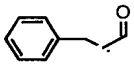
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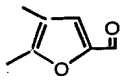
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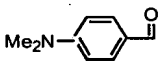
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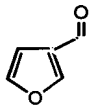
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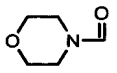
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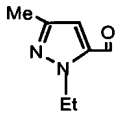
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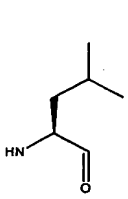
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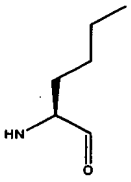
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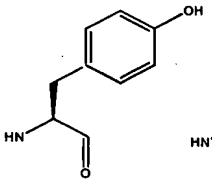
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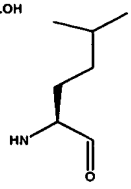
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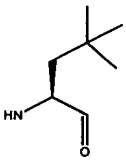

tBu-Ala

P2 Aminoacid Residues

3. K_i determinations for cathepsins S, L, and K

Cathepsin S

General

Assays were performed in 100 mM sodium phosphate, 100 mM NaCl, pH 6.5 (buffer) in white 384 well plates (Corning Costar). Eight inhibitors were assayed per plate.

Inhibitor dilutions

Inhibitor dilutions were performed on a 96 well V-bottomed polypropylene plate (Corning Costar). 100 µl of buffer was placed in wells 2-5 and 7-12 of rows A, B, C and D. Sufficient of each inhibitor at 10 mM in DMSO was placed into wells A1-D1 and A6-D6 to give the desired final concentration when the volume in the well was made up to 200 µl with buffer. Column 1 was made up to 200 µl with buffer, mixed by aspirating and dispensing 100 µl in the well, and 100 µl transferred to column 2. The pipette tips were changed and the mixing and transferral repeated to column 5. This process was repeated for columns 6-10.

Substrate dilutions

Substrate dilutions were performed on a 96 deep well polypropylene plate (Beckman Coulter). 280 µl of buffer was placed in wells B-H of columns 1 and 2. 70 µl of 10 mM boc-Val-Leu-Lys-AMC was placed in A1 and A2. 2 × 250 µl of buffer was added to wells A1 and A2, mixed by aspirating and dispensing 280 µl in the well, and 280 µl transferred to row B. The pipette tips were changed and the process repeated down the plate to row H.

Assay

Column 1 of the substrate dilution plate was distributed at 10 µl per well into alternate rows beginning at row A. Column 2 was distributed to alternate rows beginning at row B. Row A of the inhibitor dilution plate was distributed at 10 µl per well to alternate rows and columns starting at A1. Row B was

distributed to alternate rows and columns starting at A2. Row C was distributed to alternate rows and columns starting at B1 and row D was distributed to alternate rows and columns starting at B2. The assay was started by the addition of 30 µl per well of 20 nM cathepsin S in buffer containing 10 mM 2-mercaptoethanol.

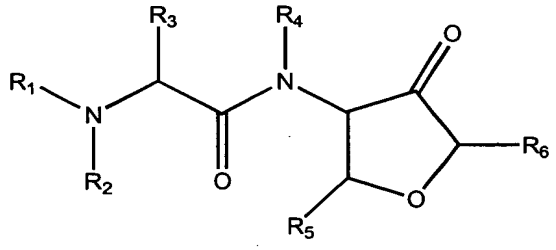
Data were saved as text files and imported into Excel. The initial rates were determined by linear regression and then fitted to the competitive inhibition equation using SigmaPlot.

Cathepsins L and K

Assays were performed essentially as above. For cathepsin L, the buffer used was 100 mM sodium acetate, 1 mM EDTA, pH 5.5 and the substrate was *D*-Val-Leu-Lys-AMC with a highest concentration of 100 µM. For cathepsin K, the buffer used was 100 mM MES/Tris, 1 mM EDTA, pH 7.0 and the substrate was *D*-Ala-Leu-Lys-AMC with a highest concentration of 250 µM.

Claims

1. A compound according to formula (II):

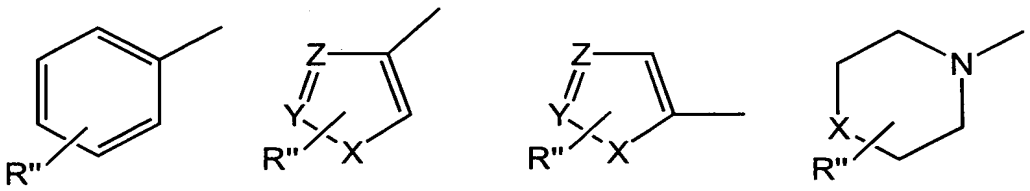


(II)

wherein:

R1 = R' , R'C(O) , R' C(S), R' SO2 , R' OC(O), R' NHC(O)

R' =



X, = O, S, NH, Y, Z = CH, N:

R'' = single or multiple ring substitution combinations taken from:

H, C1-7-alkyl, C3-6-cycloalkyl, OH, SH, NH2, Halogen;

R2, R4 = H, C1-7-alkyl, C3-7-cycloalkyl,

R3 = C1-7-alkyl, C3-7-cycloalkyl;

R5 = C1-7-alkyl, Halogen, Ar- C1-7-alkyl, C1-3-alkyl-CONR'''', R^{iv}; and

R6 = C1-7-alkyl, Ar- C1-7-alkyl; C1-3-alkyl-SO2-R^{v}, C1-3-alkyl-C(O)-NHR^{v}.

2. A compound according to claim 1 wherein 'C1-7-alkyl' is selected from the group consisting of: straight and branched chain aliphatic carbon chains such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl, heptyl and any simple isomers thereof; and any C1-7-alkyl may optionally be substituted by one or two halogens F, Cl, Br and or a heteroatom S, O, NH.

3. A compound according to claim 1 or 2 wherein 'Halogen' is selected from the group consisting of: F, Cl, Br, I.

4. A compound according to claim 1, 2 or 3 wherein 'C3-6-cycloalkyl' is selected from the group consisting of: any variation of 'C1-7-alkyl' which additionally contains a carbocyclic ring such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

5. A compound according to any of claims 1 to 4 wherein 'Ar-C1-7-alkyl' is selected from the group consisting of: any unsubstituted phenyl, pyrazolyl, imidazolyl, oxazolyl,

isoxazolyl, thiazinolyl, isothiazinolyl, thiazolyl, oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, furanyl, thienyl aromatic ring (Ar) attached through a 'C1-7-alkyl' to the dihydro-(3H)-furanone ring system; and wherein optionally, the aromatic ring may be substituted with halogen, C1-3-alkyl, OH, OC1-3-alkyl, SH, SC1-3-alkyl, NH_2, NHC1-3-alkyl, N(C1-3-alkyl)2, where C1-3-alkyl includes methyl, ethyl, propyl, isopropyl, cyclopropyl.

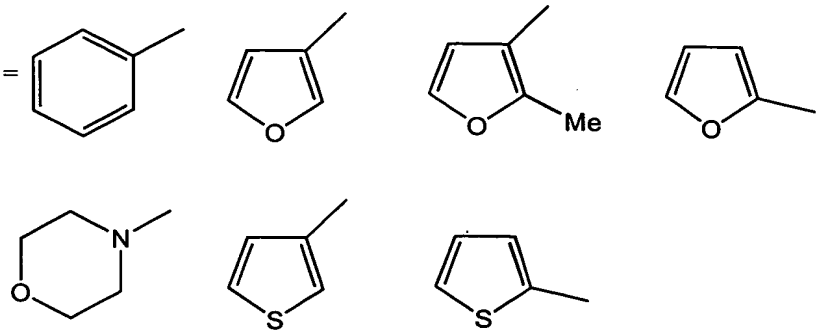
6. A compound according to any of claims 1 to 5 wherein 'C1-3-alkyl-CONR''' R^{iv}' is selected from the group consisting of: straight or branched carbon chain substituted with a 1°, 2° or 3° carboxamide wherein R''', R^{iv} includes H and Me.

7. A compound according to any of claims 1 to 6 wherein 'C1-3-alkyl-SO_2-R^v' is selected from the group consisting of: straight or branched carbon chain substituted with a sulphone wherein R^v includes 'C1-7-alkyl', 'Ar- C1-7-alkyl', 'C3-6-cycloalkyl'.

8. A compound according to any of claims 1 to 7 wherein 'C1-3-alkyl-C(O)-NHR^v' is selected from the group consisting of: straight or branched carbon chain substituted with a secondary carboxamide wherein R^v includes 'C1-7-alkyl', 'Ar- C1-7-alkyl', 'C3-6-cycloalkyl'.

9. A compound according to any of claims 1 to 8 wherein

R1 = R'C(O)

Where R' = 

R2 and R4 = H;

R3 = n-butyl, 3-(2,2-dimethylpropyl), 4-(2-methylbutyl), 4-(3,3-dimethylbutyl);

R5 = CH_3, C_2H_5, CH_2Ar, CH_2CONH_2;

R6 = H, CH_2-X-Ar, X = O, S, NH.

10. A compound according to claim 9 wherein R5 has (S) stereochemistry.

11. A compound which is selected from the group consisting of:

Dihydro-(4-(S)-Amino-N-[(3-furanoyl)-L-tButyl-L-alanine])-5-(R)-methyl)-3(2H)-furanone;

Dihydro-(4-(R)-Amino-N-[(3-furanoyl)-L-tButyl-L-alanine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(3-furanoyl)-L-tButyl-L-alanine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(3-thienoyl)-L-tButyl-L-alanine])-5-(R)-methyl)-3(2H)-furanone;

Dihydro-(4-(R)-Amino-N-[(3- thienoyl)-L-tButyl-L-alanine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(3- thienoyl)-L-tButyl-L-alanine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(3-furanoyl)-L-homoleucine])-5-(R)-methyl)-3(2H)-furanone;

Dihydro-(4-(R)-Amino-N-[(3-furanoyl)-L- homoleucine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(3-furanoyl)-L- homoleucine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(3-thienoyl)-L- homoleucine])-5-(R)-methyl)-3(2H)-furanone;

Dihydro-(4-(R)-Amino-N-[(3- thienoyl)-L- homoleucine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(3- thienoyl)-L- homoleucine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(morpholinocarbamoyl)-L-tButyl-L-alanine])-5-(R)-methyl)-3(2H)-furanone;

Dihydro-(4-(R)-Amino-N-[(morpholinocarbamoyl)-L-tButyl-L-alanine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(morpholinocarbamoyl)-L-tButyl-L-alanine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(morpholinocarbamoyl)-L-homoleucine])-5-(R)-methyl)-3(2H)-furanone;

Dihydro-(4-(R)-Amino-N-[(morpholinocarbamoyl)-L- homoleucine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(morpholinocarbamoyl)-L- homoleucine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(benzoyl)-L-tButyl-L-alanine])-5-(R)-methyl)-3(2H)-furanone;

Dihydro-(4-(R)-Amino-N-[(benzoyl)-L-tButyl-L-alanine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(benzoyl)-L-tButyl-L-alanine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(benzoyl)-L-homoleucine])-5-(R)-methyl)-3(2H)-furanone;

Dihydro-(4-(R)-Amino-N-[(benzoyl)-L- homoleucine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(benzoyl)-L- homoleucine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(3-(2-methyl)furanoyl)-L-tButyl-L-alanine])-5-(R)-methyl)-3(2H)-furanone;

Dihydro-(4-(R)-Amino-N-[(3-(2-methyl)furanoyl)-L-tButyl-L-alanine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(3-(2-methyl)furanoyl)-L-tButyl-L-alanine])-5-(S)-methyl)-3(2H)-furanone;

Dihydro-(4-(S)-Amino-N-[(3-(2-methyl)furanoyl)-L-homoleucine])-5-(R)-methyl)-3(2H)-furanone;

Dihydro-(4-(R)-Amino-N-[(3-(2-methyl)furanoyl)-L-homoleucine])-5-(S)-methyl)-3(2H)-furanone;

and

Dihydro-(4-(S)-Amino-N-[(3-(2-methyl)furanoyl)-L-homoleucine])-5-(S)-methyl)-3(2H)-furanone,

or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising a compound according to any preceding claim and a pharmaceutically acceptable carrier.

13. A method of inhibiting the cysteine protease Cathepsin S which comprises administering to a patient in need thereof an effective amount of a compound according to any of claims 1 to 11.

14. A method of inhibiting the cysteine protease Cathepsin S which comprises administering to a patient in need thereof an effective amount of a composition according to claim 12.

15. Use of a compound according to any of caims 1 to 11 in the manufacture of a medicament for the treatment of a desease in which inhibition of Cathepsin S cysteine protease activity is a factor.